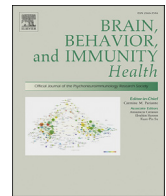


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Full Length Article

Self-reported cognitive impairment in individuals with Primary Immunodeficiency Disease

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ABSTRACT

Individuals with Primary Immunodeficiency Disease (PID) have increased risk for infection, autoimmune conditions, and inflammatory disorders. Cognitive impairment, also referred to as brain fog, has been recognized in other medical conditions and as a side-effect of treatments; however, it has not been previously reported in individuals with PID. The phenomenon of brain fog is recognized in other autoimmune or inflammatory conditions, including lupus, multiple sclerosis, chronic fatigue syndrome, and has resulted from chemotherapy treatment for cancer. This research investigates the self-reported memory function of individuals with a diagnosis of PID. Respondents completed a survey which used reliable and valid questionnaires: Memory Functioning Questionnaire, Beck's Depression Inventory II, and Beck's Anxiety Inventory. Of the 292 completed surveys, 133 did not report any comorbid neurological diagnosis or incident of concussion (both of which could influence perceived memory function). When compared to normative scores, the respondents in this study were found to have significantly greater perceived memory impairment. The respondents had a significant higher score for anxiety and depression as compared to non-anxious and non-depressed normative values. This study finds that individuals with a diagnosis of PID have a greater degree of perceived memory impairment, or brain fog, in addition to greater levels of anxiety and depression. Individuals with a diagnosis of PID would benefit from prospective surveillance through a comprehensive neuropsychological assessment to track cognitive status and implement corrective measures, should any decline be identified.

1. Background

Primary immunodeficiencies (PID) are rare genetic conditions that result in an increased susceptibility to infections, autoimmune conditions, inflammatory disorders, and malignancies (Tangye et al., 2020). The 2019 update from the International Union of Immunological Societies Expert Committee (IUIS) has identified 430 inborn errors of immunity under the umbrella of PID (Tangye et al., 2020). There is much published research concerning the medical conditions associated with PID and the optimal treatment of PID (Abolhassani et al., 2012; Jolles et al., 2015; Jones et al., 2018; Shrestha et al., 2019). There is also a growing volume of literature related to quality of life for individuals who are diagnosed with PID (Anterasian et al., 2019; Jiang et al., 2015; Peshko et al., 2019; Quinti et al., 2012). However, the literature investigating neurological integrity and cognitive status of individuals

diagnosed with PID is sparse.

Cognitive impairment, especially related to functional memory, has not been previously reported in the PID population. There is one report of neurodegenerative changes in the PID population (Ziegner et al., 2002). The issue of memory impairment is recognized in many other autoimmune or inflammatory conditions, including lupus (Kalim et al., 2020), multiple sclerosis (Macias Islas and Ciampi, 2019), chronic fatigue syndrome (Ocon, 2013; Rasouli et al., 2019), and has also been linked to chemotherapy treatment for cancer (El-Agamy et al., 2019; Sordillo and Sordillo, 2020). The complexity of this change in cognition may be multifactorial.

Brain fog is an aspect of neurocognitive impairment, commonly seen with infectious or inflammatory conditions, that “clouds mentation and limited attentional capacity” and is a major factor in the disability associated with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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(Hornig, 2020, p. 1102). Komaroff and Buchwald (1991) investigated the impaired cognition reported by individuals diagnosed with Chronic Fatigue Syndrome. Patients reported the cognitive impairment to be especially debilitating as it resulted in lack of concentration and attention, impaired verbal expression, and absentmindedness (Komaroff and Buchwald, 1991). Ross et al. (2013) surveyed individuals with a diagnosis of postural tachycardia syndrome (POTS) and 132 of 138 respondents, reported brain fog. The authors described brain fog as a cognitive impairment, similar to mental fatigue that impairs performance on cognitive tasks. Respondents in the study described their brain fog as: forgetful, cloudy, and difficulty focusing, thinking, and communicating (Ross et al., 2013). Similarly, cancer survivors report brain fog, often referred to as “chemo brain” (Kovalchuk & Kolb, 2017). Research has found that chemotherapeutic drugs cause side effects resulting in impairments in the cognitive domains of memory, attention, processing speed, and executive function (Kovalchuk & Kolb, 2017).

In PID, neurologic issues may occur due to infectious, autoimmune, or malignant pathologies. Some PIDs, such as ataxia-telangiectasia and purine nucleoside phosphorylase (PNP) deficiency have neurologic involvement as a diagnostic feature (Yildirim et al., 2018). There are a number of PIDs that involve primary or secondary neurological manifestations, such as: microcephaly, developmental delay, motor system dysfunction, ataxia, seizure, tremor, neuropathy, or behavioral issues (Dehkordy et al., 2012). A retrospective analysis by Ziegner et al., in 2002 identified 14 patients with PID and a progressive neurodegenerative disease of unknown etiology. In all 14 patients, CT or MRI identified brain atrophy with prominent sulci and enlarged ventricles; 11 of 13 patients had abnormal EEGs with slow waves and/or epileptiform activity; and 6 of 14 patients had abnormal CSF (Ziegner et al., 2002). No clear cause of the progressive neurodegenerative disease was identified in the retrospective study. A prospective study by Jassen et al. (2018) found that patients with unclassified primary antibody deficiency were coping with “pain, negative feelings, and impairments in cognition, home management tasks, sleep, social interaction, and work” (p. 6).

Individuals with mild cognitive impairment are often impacted by anxiety and depression (Ma, 2020; Mirza et al., 2017). Because of this, it is important to assess anxiety and depression when screening for cognitive impairment in any patient population. Heath et al. (2016) conducted a pilot study to investigate the prevalence of anxiety and depression in adult individuals with PID using an investigator-developed survey along with the Hamilton Depression Rating Scale and the Hamilton Anxiety Scale. In this sample, the participants with PID had similar levels of depression and anxiety as compared to the U.S. population; there were several factors related to their diagnosis and treatment that contributed to elevated scores in various subgroups. A study by Kuburovic et al. (2014) found that children with a diagnosis of PID are at a significantly greater risk for demonstrating symptoms of depression and anxiety. This purpose of this research survey was to investigate the incidence of self-reported cognitive impairment, or brain fog, in individuals with a diagnosis of PID.

2. Sample & methods

This research was approved by the Institutional Review Board at Stockton University. Informed consent was obtained through the first question of the online survey. Individuals 18 years or older with a diagnosis of PID were eligible to participate. The Qualtrics survey platform was used to create and distribute the survey. The survey was available through an anonymous link from July to September of 2019. It was distributed through multiple public and private social media patient support groups. Participants were asked to complete the survey only one time. It was estimated that it would take 25–35 min to complete the survey. Some questions allowed only one response while others permitted multiple responses. The survey was designed to be compatible with any mobile device (such as a tablet, or smartphone) and a computer. Fourteen screens were used to complete the survey; questions were not

randomized. Participants were able to change prior responses and could return to the survey if they were unable to complete in one sitting. To improve face validity, the survey was initially sent to several individuals without a PID diagnosis and individuals with a diagnosis of PID, to test the survey platform and provide feedback on survey flow.

The survey consisted of initial demographic inquiries, questions to assess medical history relating to neurological conditions, and three psychometrically tested questionnaires. The three validated questionnaires included the Memory Functioning Questionnaire (MFQ), Beck Depression Inventory II (BDI-II), and Beck Anxiety Inventory (BAI). The MFQ was developed for “assessment of self-perceptions of memory abilities” (Gilewski et al., 1990, p.482) and has good psychometric properties (Gilewski et al., 1990, p.482). The MFQ consists of 64-item scale that is rated on a 7-point scale allowing for the calculation of factor scores for four categories (Zelinski et al., 1990). The internal consistency of the factor scores is high, based on alpha scores from 0.94 to 0.83 (Zelinski et al., 1990). Parisi et al. (2011) found that the changes in the report of frequency of forgetting was associated with change in objective memory performance; this is consistent with similar findings from Lane and Zelinski in 2003. The MFQ factors have been found to be independent of age, education, or self-reported health issues (Gilewski et al., 1990, p.482) and independent of each other (Lane and Zelinski, 2003). Zelinski et al. (1990) found that Frequency of Forgetting and Seriousness of Forgetting were the most useful for predicting the results of clinical memory tests. The authors note there is a relationship between Frequency of Forgetting and depressive symptoms (Zelinski et al., 1990). Due to the observed connection between cognitive impairment and anxiety and depression in the literature (Mizra et al., 2017), it is also important to assess these domains in participants living with PID. Thus, two psychometrically established scales, the Beck Depression Inventory II (Wang and Gorenstein, 2013) and the Beck Anxiety Inventory (Beck et al., 1988) were used in this study. Beck et al. (1988) found that the BAI demonstrates high internal consistency, test-retest reliability, ability to discriminate between anxious and non-anxious diagnostics groups, and correlation to other scales of anxiety. Wang and Gorenstein (2013) found that the BDI-II demonstrates high reliability, capacity to discriminate between depressed and non-depressed subjects, and improved concurrent, content, and structural validity.

Data from the participant responses for the MFQ, BDI-II, and BAI were compared to established normative values. Zelinski et al. (1990) provide normative data for the MFQ from a sample of older adults, ages 55–85 years; this normative data was from 198 older adults drawn from a sample of 772 individuals participating in a psychometric study of adult intelligence was used for comparison of the results. The normative data from Zelinski et al. (1990) provides a value of 158.13 ± 28.42 (maximum score of 231) for the Frequency of Forgetting subscale; 84.60 ± 21.53 (maximum score of 126) for the Seriousness of Forgetting subscale; 17.04 ± 6.06 (maximum score of 35) for the Retrospective Functioning subscale; and 28.97 ± 11.56 (maximum score of 56) for the Mnemonics Usage subscale [32]. A higher score reflects a higher level of perceived memory functioning (fewer forgetting incidents, less serious incidents, improvement of memory ability relative to earlier life, and less use of mnemonics) while a lower score suggests worse perceived memory issues. Beck et al. (1988) determined the psychometric properties of the BAI. For the BAI, normative score for an adult control group ($n = 16$) was 15.88 ± 11.81 while the normative score for adults with a pure anxiety diagnosis ($n = 82$) was 24.59 ± 11.41 (Beck et al., 1988). For the BDI-II, the normative score for college students (control group, $n = 120$) was 12.60 ± 9.90 , while the normative score for psychiatric outpatients ($n = 500$) was 22.50 ± 12.80 (Wang and Gorenstein, 2013).

Data analysis was completed using SPSS version 25 and analyzed using a one-sample *t*-test, comparing the collective survey results to normative values available from published literature for the MFQ, BAI, and BDI-II. The alpha level was set to 0.05.

Table 1
Participant demographics.

Participants	All Surveys	Non-Neuro
	n = 292	n = 133
Gender % (n)		
Male	2.7 (8)	1.5 (2)
Female	95.2 (278)	95.5 (127)
Other/Prefer not to identify	2.1 (6)	3.0 (4)
Age % (n)		
18–29 years	4.1 (12)	3.8 (5)
30–44 years	26.0 (76)	27.1 (36)
45–64 years	54.5 (159)	53.4 (71)
65 years and older	15.4 (45)	15.8 (21)
Ethnicity % (n)		
White/Caucasian	95.5 (279)	92.5 (123)
Hispanic/Latino	3.1 (9)	5.3 (7)
Native American/American Indian	0.7 (2)	0.8 (1)
Other	0.7 (2)	1.5 (2)
Education % (n)		
Professional Degree	2.4 (7)	2.3 (3)
Doctorate Degree	4.1 (12)	4.5 (6)
Some high school, no Diploma	0.3 (1)	0.0 (0)
High school graduate or equivalent	6.2 (18)	6.8 (9)
Some college credit, no degree	18.2 (53)	22.6 (30)
Trade/technical/vocational Training	7.5 (22)	10.5 (14)
Associate Degree	8.9 (26)	5.3 (7)
Bachelor Degree	32.2 (94)	32.3 (43)
Master Degree	20.2 (59)	15.8 (21)

3. Results

A total of 363 responses were collected; 292 were complete, without any missing data. The specific type of PID diagnosis was self-reported by the participants. A targeted question in the survey asked about the history of a neurological diagnosis (such as traumatic brain injury, cerebrovascular accident, dementia, multiple sclerosis, or other), while another question asked participants if they had any history of concussion. Since neurological diagnoses and concussions may both impact memory, additional analysis was done for 133 completed surveys with no reported history of neurological diagnosis or concussion.

Participant demographics of both samples are presented in **Tables 1 and 2**.

Table 3 identifies the responses for the questions about neurological diagnosis and concussions.

Table 4 highlights the results of the one-sample t tests used to compare the normative values of the MFQ, BAI, and BDI-II scales to the mean score for the participants, using all completed surveys and surveys that indicated no prior neurological event. The normative values used for the MFQ were: 158.13 for the subscale of Frequency of Forgetting; 84.60 for the subscale of Seriousness of Forgetting; 17.04 for the subscale of Retrospective Functioning; and 28.97 for the subscale of Mnemonics Usage (Zelinski et al., 1990). The non-anxiety normative value for the BAI was 15.88, while those diagnosed with anxiety are represented by a normative value of 24.59 (Beck et al., 1988). The non-depressed normative value for the BDI-II was 12.60, while psychiatric outpatients are represented by a normative value of 22.50 (Wang & Gorenstein, 2013a, 2013b).

4. Discussion

For the MFQ, higher scores reflect greater levels of perceived memory functioning (fewer and less serious forgetting incidents, improvement of memory ability relative to earlier in life, and less use of mnemonics), while lower scores suggest worse memory function (Zelinski et al., 1990). For both samples (all completed surveys and those without a neurological

Table 2
Health-related demographics.

Participants	All Surveys	Non-Neuro
	n = 292	n = 133
Type of PID % (n)		
CVID	81.5 (238)	80.5 (107)
SAD	7.5 (22)	9.0 (12)
IgG Subclass Deficiency	4.5 (13)	3.8 (5)
XLA	0.7 (2)	0.8 (1)
Selective IgA Deficiency	0.3 (1)	0.0 (0)
Hyper IgM Deficiency	0.3 (1)	0.8 (1)
CGD	0.3 (1)	0.0 (0)
Other	4.8 (14)	5.3 (7)
Time Diagnosed % (n)		
< 1 year	11.6 (34)	13.5 (18)
1–5 years	40.4 (118)	42.1 (56)
6–10 years	24.7 (72)	15.8 (21)
11–15 years	10.6 (31)	10.5 (14)
> 15 years	12.7 (37)	18.0 (24)
Treatment % (n)		
No Treatment	7.9 (23)	8.3 (11)
IVIG	27.4 (80)	27.1 (36)
SCIG	50.7 (148)	51.9 (69)
Antibiotics	1.7 (5)	1.5 (2)
Other	2.4 (7)	3.0 (4)
Combination	9.9 (29)	8.3 (11)
Mental Health % (n)		
Anxiety	13.0 (38)	10.5 (14)
Depression	13.7 (40)	9.8 (13)
Other	1.0 (3)	1.5 (2)
Anxiety & Depression	32.2 (94)	28.6 (38)
Anxiety, Depression & Other	6.5 (19)	6.8 (9)
Anxiety & Other	1.0 (3)	1.5 (2)
None	32.5 (95)	41.4 (55)

Note. CVID = Common Variable Immune Deficiency; SAD = Specific Antibody Deficiency; XLA = X-linked Agammaglobulinemia; CGD = Chronic Granulomatous Disease; IVIG = Intravenous IgG replacement; SCIG = Subcutaneous IgG replacement.

Table 3
Neurological Conditions and Concussions.

Participants	n = 292
Neurological Diagnoses % (n)	
None	80.8 (236)
TBI/ABI	2.1 (6)
CVA	0.7 (2)
Other	13.7 (40)
Multiple diagnoses	2.7 (8)
Concussions % (n)	
1 concussion	17.1 (50)
> 1 concussion	16.8 (49)
Not dx, suspect 1 concussion	10.3 (30)
Not dx, suspect > 1 concussion	3.4 (10)
None	52.4 (153)

Note. TBI = Traumatic Brain Injury; ABI = Acquired Brain Injury; CVA = Cerebrovascular Accident.

issue), the MFQ Frequency of Forgetting subscale was significantly lower than the normative score, indicating the individuals with a diagnosis of PID experienced more frequent forgetfulness as compared to older adults (55–85 years old). For both samples (all completed surveys and those without a neurological issue), the MFQ Seriousness of Forgetting subscale was significantly lower than the normative score, indicating the individuals with a diagnosis of PID experienced more memory failures as compared to older adults (55–85 years old). For both samples, the MFQ Retrospective Functioning subscale was significantly lower than the

Table 4
MFQ, BAI, & BDI-II results.

Participants	All Surveys	Non-Neuro
	n = 292	n = 133
MFQ (M ± SD)		
<i>Frequency of Forgetting</i>	133.89±38.93 (p = .000)	133.89±39.11 (p = .000)
<i>Seriousness of Forgetting</i>	67.07±25.76 (p = .000)	67.88±26.30 (p = .000)
<i>Retrospective Functioning</i>	13.22±6.23 (p = .000)	13.19±5.88 (p = .000)
<i>Mnemonics Usage</i>	18.86±8.77 (p = .000)	19.32±9.49 (p = .000)
BAI (M ± SD)	21.69±13.90	20.25±12.82
Non-anxiety Comparison	p = .000	p = .000
Anxiety Comparison	p = .000	p = .000
BDI (M ± SD)	19.22±12.15	19.13±11.32
Non-depressed Comparison	p = .000	p = .000
Psychiatric Comparison	p = .000	p = .001

normative score, indicating the individuals with a diagnosis of PID experienced greater recent changes in memory function as compared to older adults (55–85 years old). For both samples, the MFQ Mnemonics Usage subscale was significantly lower than the normative score, indicating the individuals with a diagnosis of PID experienced greater dependency on the use of mnemonics as compared to older adults (55–85 years old).

The BAI is a valid and reliable scale that measures anxiety without being confounded by depression (Beck et al., 1988). A higher score on the BAI indicates a higher degree of anxiety. A score of 0–7 represents minimal anxiety, 8–15 mild anxiety, 16–25 moderate anxiety, and 26–63 severe anxiety (Bardhoshi et al., 2016). For both samples (all completed surveys and those without a neurological issue) the BAI was significantly higher than the normative score for those without anxiety. However, the score on the BAI for both samples was significantly lower when compared to normative scores of individuals diagnosed with anxiety. Additionally, the BAI scores of 21.69±13.90 (all completed surveys) and 20.25±12.82 (non-neuro completed surveys) indicates moderate anxiety in this population.

For the BDI-II, higher scores are suggestive of more significant depression. A score of 0–13 represents minimal depression, 14–19 mild mood disturbance, 20–28 moderate depression, and greater than 29 indicates severe depression (Wang and Gorenstein, 2013b). For both samples (all completed surveys and those without a neurological issue) the BDI was significantly higher than the normative score for a control group of college students (no depression). However, the score on the BDI-II for both samples was significantly lower when compared to normative scores of a psychiatric outpatient population. Additionally, the BDI-II scores of 19.22±12.15 (all completed surveys) and 19.13±11.32 (non-neuro completed surveys) would fall on the borderline between mild mood disturbance and moderate depression.

The MFQ assesses perceived memory impairment, which may differ from neuropsychological assessment of clinically measurable short- or long-term memory function. Further assessment testing is needed to determine consistency in perception of memory impairment with measurable memory loss or decline. This survey was only distributed through social media platforms which precludes individuals with limited access to technology. Social media is very useful due to its speed, low cost, and accessibility to reach rare diagnoses, but there is a tendency for sampling using social media to have an overrepresentation of young, white females (Whitaker et al., 2017). Stern et al., (2017) found that participants who were recruited through Facebook were more likely to be white, higher educated, and have a higher income compared to those recruited through Google. Those who responded may have identified with the concept of brain fog, thus causing a potential overestimation of the findings. Batterham (2014) found that people with a mental health problem are more likely to complete mental health surveys and that this response rate appeared to be amplified for online surveys. Respondents

were predominantly white females, between the ages of 30–64 years, with a diagnosis of Common Variable Immune Deficiency, thus the survey is limited in its generalizability. Further research is needed to address a broader representation of gender, race, and ethnicity and determine if this perception of memory impairment is reported throughout the broader PID community. The survey was only available to adults, so additional research on memory and cognitive impairment in children is needed.

These results indicate that individuals diagnosed with PID may benefit from a comprehensive neuropsychological assessment that includes an evaluation of overall mental health. This would further elucidate the specific areas of cognition affected (e.g., attention, encoding of information, retrieval of information, executive functioning). The overall pattern of performance on neuropsychological and psychosocial measures may assist in definitively determining the extent to which depression and anxiety may impact cognitive functioning. While many studies of brain fog utilize brief screening tools, a more detailed evaluation is recommended. The combination of neurocognitive testing and assessment of mental health status may also determine if some individuals with PID are meeting the diagnostic criteria for major depressive disorder, an anxiety disorder, and/or mild or major neurocognitive disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). A detailed neurocognitive assessment would be necessary to help separate the issue of self-reported memory impairment from an underlying issue of depression and/or anxiety. Proper diagnosis of any and all of these conditions is the first step in enhancing one's quality of psychosocial and cognitive functioning within the context of PID.

5. Conclusion

Individuals with a diagnosis of PID demonstrate significant perceived memory impairment, moderate anxiety, and mild to moderate depression when compared to normative scores for those without any clinically diagnosed memory impairment, anxiety, or depression. There is paucity in the literature on this phenomenon for individuals with PID and further research is needed to optimize quantitative assessment for proper differential diagnosis. In addition, further exploration is warranted to ascertain best practices through specific interventions for PID with neurocognitive and mental health needs.

Prospective surveillance in the form of a comprehensive neuropsychological assessment, including an assessment of overall mental health, should be recommended to individuals with PID who report symptoms of cognitive impairment, anxiety, or depression. This assessment should include an interprofessional team approach to diagnose and leverage a holistic approach to manage symptoms of cognitive impairment in this population.

Compliance with ethical standards

This research study was IRB approved by Stockton University.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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